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|---|---|
| JAGOE, DONNA A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/734,070 | ZAPPALA, STEPHEN M. | |
| | Examiner | Art Unit | |
| | Donna Jagoe | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The amendment filed 28 November 2005 has been received and entered. Claims 9 and 26-34 have been amended. Claims 1-34 are pending in this application.

***Response to Amendment***

Objection to claim 9 for spelling errors is no longer maintained in view of the amendment.

Objection to claim 28 is no longer maintained due to the amendment.

Rejection of claims 9 and 31-34 under 35 U.S.C. §112 2nd paragraph is no longer maintained in view of the amendment.

***Response to Arguments***

Applicant's arguments filed 28 November 2005 have been fully considered but they are not persuasive. The rejection made in the paper mailed 1 March 2005 under 35 U.S.C. §103(a) is maintained and hereby repeated for the reasons set forth in the previous office action and those set forth below.

Claims 1-8 and 16-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seow et al., Miller Goodman and Gilman(U) and Cousins.

Seow et al. teach administration of 2% lidocaine and 0.5% bupivacaine in a mixture for epidural blockade in ratios of from 3:1 to 1:3 which overlaps and encompasses the claimed ranges. Further, regarding the claims ranges of less than 10:1, one skilled in the art would have been motivated to prepare additional useful compositions of the ranges taught by the prior art. While the reference is silent

regarding some % ratios, the difference in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. When the general conditions are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 45, 105 USPQ 233, 235 (CCPA 1955). In the absence of any criticality and/or unexpected results of the additional ranges claimed, instant invention is considered obvious. The anesthetic agents contained 1:200,000 epinephrine (a vasoconstrictor) (see abstract).

Duration of action of the lidocaine and bupivacaine is 286 ± 32 minutes (see Seow abstract). This differs from the claimed "at least 6 hours" however, Goodman and Gilman teaches the duration of action and peak concentrations of local anesthetics in blood depends upon the amount injected, the physical characteristics of the local anesthetic and whether epinephrine is used. They are also determined by the rate of blood flow to the site of injection (page 313, column 1). By adding epinephrine, the duration can be approximately doubled by decreasing the rate of absorption of drug into the blood stream (see page 311, columns 1-2). Further, Goodman and Gilman teaches that Goodman and Gilman teach that the latency of the anesthetic effect of lidocaine injected about the ulnar nerve is 3 minutes, but this value is nearly 15 minutes when the drug is injected about the brachial plexus (page 312, column 2) so it also depends on the site of administration. Goodman and Gilman teach the duration of action of bupivacaine is 400 to 450 minutes and the duration of action of lidocaine is 60 to 120 minutes (page 312, column 2). Thus it would have been obvious to one of ordinary skill

in the art to vary the aliquot of lidocaine to bupivacaine and to add or exclude epinephrine to increase or decrease the duration of action of the anesthetic motivated by the teachings of Goodman and Gilman as described above and in Chapter 15 of the Pharmacologic Basis of Therapeutics.

Seow does not teach the combination of 1% lidocaine and 0.25% bupivacaine, however, Miller discloses that to create an epidural blockade, the "usual concentration" range for lidocaine is 1-2% and the "usual concentration" range for bupivacaine is 0.25% to 0.75% (page 506, table 15-7). It would have been made obvious to one of ordinary skill in art at the time it was made to create a rapid-onset, long acting anesthetic motivated by the teaching of Seow et al. who teach lidocaine-bupivacaine combination and the teachings of Miller wherein the concentrations of lidocaine and bupivacaine are selected from the range of usual concentrations.

Goodman and Gilman further teach that in practice, local anesthetics such as lidocaine, which act rapidly but relatively briefly, are **often** combined with an anesthetic such as bupivacaine, which although slow in onset, has a long duration of action.

Cousins provides the motivation to buffer the anesthetic solution wherein it is disclosed that sodium bicarbonate will increase the pH of the local anesthetic solution, which in turn will increase the amount of the drug in the uncharged base form. Thus the rate of diffusion across the nerve sheath and nerve membranes should be enhanced resulting in a more rapid onset of anesthesia. Sodium bicarbonate was added to bupivacaine resulting in a significant decrease in the latency of brachial plexus blockade and it is reported that the duration of anesthesia was prolonged by increasing the pH of

the local anesthetic solution (page 105, column 1, first paragraph). It does not teach the specific buffers sodium hydroxide and hydrochloric acid; however, the net effect would be the same by the addition of the buffers sodium hydroxide and hydrochloric acid, an increase to the pH to 7.4. Additional motivation is provided for the pH of 7.4 because that is the normal pH of human blood and spinal fluid. It would have been obvious to buffer to a pH of 7.4 motivated by the desire for a faster latency period and longer duration of action as disclosed by Cousins.

2. Claims 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seow et al., Miller, Goodman and Gilman(U) and Cousins as applied to claims 1-8 and 16-34 above, and further in view of Ko et al.

Ko et al. teach a method for reducing perioperative pain by injecting a preemptive analgesic solution before incision, wherein the preemptive analgesic used is a 1:1 mixture of 1% lidocaine and 0.5% bupivacaine (page 875). The preincisional injection technique of Ko is infiltration into the dermis and subcutaneous tissues (page 875, column 2, line 1). Although the concentration of Ko et al. was 1% lidocaine and 0.5% bupivacaine HCl, it is disclosed that there may be an advantage to using a larger volume of more diluted anesthetic agents, by diluting the concentration of local anesthetic agents, greater volumes can be used. Greater volumes would be more effective than smaller volumes of more concentrated agents because a larger tissue area may be anesthetized. It would have been made obvious to one of ordinary skill in art at the time it was made to employ a more dilute solution of bupivacaine in the

mixture of lidocaine and bupivacaine. Such a modification would have been motivated by the reasoned expectation of producing an anesthetic composition which is effective in comprehensively producing preemptive anesthesia to greater areas of tissue in a patient as recited by Ko et al. above.

In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention. This motivation may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. Here, filtered through the knowledge of one skilled in the art, the prior art disclosed that lidocaine is available in a concentration of 1% and bupivacaine is available in a concentration of 0.25% and both are available with epinephrine 1:200,000. It is also disclosed in the prior art that lidocaine has a short duration of action and short latency period and bupivacaine has a longer duration of action and a longer latency period. The prior art teaches that these agents are frequently combined because a shorter latency period and longer duration of action is desired in some surgical procedures. It is further disclosed by the prior art that bupivacaine has a duration of action of about 400 to 450 minutes (at least 6 hours). In addition, by the time of the claimed invention, lidocaine and bupivacaine were well-known and successful local anesthetic agents, and were frequently combined. Accordingly, there was clear motivation to combine the lidocaine and bupivacaine to produce a shorter latency period and longer duration of action.

Applicant asserts that Seow et al. do not teach the claimed percentage of 1% lidocaine and 0.25% bupivacaine, but Miller discloses that the usual concentration of lidocaine is 1-2% and the usual concentration of bupivacaine is 0.25 to 0.75%, but Miller does not suggest combining the two anesthetics. In response, Goodman and Gilman further teach that in practice, local anesthetics such as lidocaine, which act rapidly but relatively briefly, are **often** combined with an anesthetic such as bupivacaine, which although slow in onset, has a long duration of action. This case comes very close to the reasoning in *EMI Group North America, Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342 [60 USPQ2d 1423] (Fed. Cir. 2001). In that case, this court explained that people had used fires for thousands of years before the first discovery of oxygen as a component of combustion. The first discoverer of the role of oxygen could not have hypothetically claimed a method of making fire with oxygen. *Id.* at 1351. Similarly, the instant invention that claims a combination of 1% lidocaine and 0.25% bupivacaine cannot withdraw some anesthetic compositions from the public domain by explaining or purporting to claim the specific ratios and the scientific underpinnings of their operation. To constitute the public use of an invention it is not necessary that more than one of the patent articles should be publicly used. The use of a great number may tend to strengthen the proof, but one well defined case of such use is just as effectual to annul the patent as many." Likewise, it is not necessary that more than one person use the invention. Egbert v. Lippmann, 104 U.S. 333, 336 (1881). Goodman and Gilman states that in practice, local anesthetics such as lidocaine, which act rapidly but relatively briefly, are **often** combined with an anesthetic such as bupivacaine, which although

slow in onset, has a long duration of action. The amounts combined are usually adjusted to the locus being treated.

Applicant submits further evidence of patentability by submitting that there are no other commercialized embodiments of the reference. Applicant's argument is itself insufficient to outweigh the record of evidence of a *prima facie* case of obviousness, since failure to present any other objective evidence of non-obviousness rebuts the assertion that the composition actually satisfied long felt need within the industry.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

### *Conclusion*

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

### *Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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01/05/2006

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